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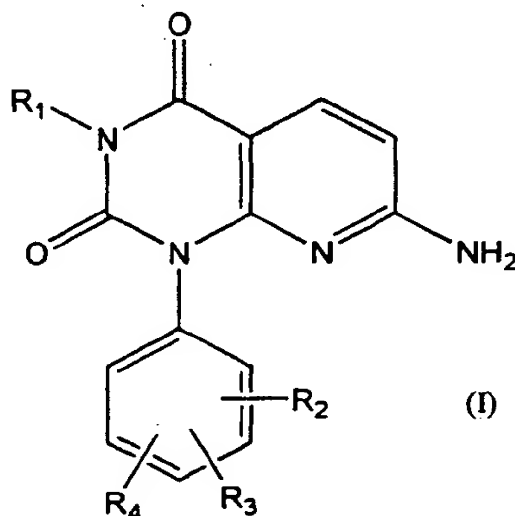
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(54) **7-Aminopyrido(2,3-d)-pyrimidine derivatives for treatment of bronchial asthma**

(57) The invention provides 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivatives of the formula (I) or a pharmaceutically acceptable salt or hydrate thereof;



wherein

R₁ is hydrogen, lower alkenyl, phenyl or optionally substituted lower alkyl which is optionally substituted with a substituent selected from oxo; lower alkoxy; phenyl which is optionally substituted with one or more lower alkyl, lower alkoxy, carboxyl, lower alkoxycarbonyl, mercapto, halogen, trifluoromethyl and/or nitro; naphthyl; furyl; isoxazolyl which is optionally substituted with one or more lower alkyl; pyridyl which is optionally substituted with one or more lower alkyl and/or halogen; thienyl which is optionally substituted with halogen; and 1,3-dioxolanyl; and R₂, R₃ and R₄ each independently is hydrogen, halogen, lower alkoxy, benzyloxy, carboxyl or lower alkoxycarbonyl, which is useful for a therapeutic agent for bronchial asthma by exhibiting excellent bronchial dilating action as well

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as high safety and a favorable behavior *in vivo*.

Description

Technical Field of the Invention

- 5 [0001] The present invention relates to a novel 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivative and a medical use thereof.

Prior Art

- 10 [0002] Allergy is a pathological condition where living body is damaged by an immune response though the response is originally a biological defense reflex. Allergic rhinitis is divided broadly into two groups. Namely, one is perennial rhinitis caused by house dust or by mite and another is pollinosis linked with a lot of pollen flying whereby many patients are generated as well. There is a difference in symptoms between those allergies and, therefore, therapeutic method is different. But, when once a person is suffered from the disease, natural healing at an early stage cannot be
15 expected and no therapeutic method to cure completely has been established yet. Therefore, numbers of patients are cumulatively increasing.

- [0003] Bronchial asthma is a disease which is characterized in a paroxysmal dyspnea accompanied by coughs and wheezes. Although its cause is ambiguous, a concept that it is a chronic inflammatory disease of airway has been established recently in addition to the already proposed concept of reversible obstructive impairment and hypersensitivity of airway. Accordingly, in the current therapy, steroidal preparations are used with an object of suppression of
20 inflammation of airway and, since the diseases is also accompanied by an airway obstruction, anti-chemical mediators or bronchial dilators are used jointly.

- [0004] Steroidal preparations used by means of inhalation, oral administration, intravenous injection, etc. are the pharmaceuticals which express various side effects together with a sharp clinical effect and, with regard to main side
25 effects, induction of infectious diseases, osteoporosis, arteriosclerosis, diabetes mellitus, mental disorder and moon face are known. It is said that serious side effect occurs when administration of steroidal preparation extends over a long period and that frequency and degree of seriousness of adrenal insufficiency is dependent upon the dose and term of the administration. Especially, the withdrawal symptom occurred by a rapid reduction of the administering dose and the adrenal insufficiency by adrenal cortical shrinkage due to administration of high dose for a long period are said to
30 be problems.

- [0005] Anti-chemical mediators are the pharmaceuticals which inhibit the biosynthesis and liberation of chemical mediators participating in allergy such as histamine, thromboxane and leukotriene, or the pharmaceuticals which antagonize the binding of such chemical mediators to the receptors. Thus, such anti-chemical mediators are not the direct therapeutic agents for dilating the shrunk airway of asthma and for improving the dyspnea but are used as the pharmaceuticals for preventing the onset of asthma symptoms caused by chemical mediators.
35

- [0006] Bronchial dilators are β_2 stimulants and theophylline preparations which are used as rapid-acting therapeutic agents for relieving the dyspnea symptom upon asthma and, in the case of onset of severe asthma, therapies such as a subcutaneous injection of β_2 stimulant and a continuously intravenous drip of theophylline are carried out. However, in the treatment of β_2 stimulant, there is a problem of death by suffocation from a negative feedback due to its abuse.
40 The theophylline preparation also has a disadvantage that its safety region is narrow and that, at high concentrations, occurrence of toxic symptoms, headache, vomiting, pulsation and extrasystole takes place. Because of those reasons, at present, caution for abuse is required for β_2 stimulants, and a therapeutic drug monitoring (TDM) is carried out for theophylline preparations.

- [0007] As mentioned above, the already-known therapeutic agents for bronchial asthma have both merits and demerits in terms of onset of the effect and generation of the side effect. And, therefore, in the practical clinical field, there has been a demand for the pharmaceuticals having higher safety and more rapidly acting property.

- [0008] It has been reported already that the known compounds having a similar pyrido[2,3-d]pyrimidine structure to the compounds of the present invention have an anti-allergic action (Japanese Laid-Open Patent Publication Sho-63/45279). It has been also known that the compounds having a 7-aminopyrido[2,3-d]pyrimidine structure show a bronchial dilating action (Japanese Laid-Open Patent Publications Hei-8/3046, Hei-8/3164 and Hei-8/3165). However, in those known compounds, separation of pharmaceutical effect from side effect is not sufficient and, with regard to the bronchial dilating action, they are not satisfactory as well whereby they have not been allowed as the pharmaceuticals for actual use. Besides the above-mentioned ones, various compounds having a pyrido[2,3-d]pyrimidine structure have been reported (refer, for example, to Japanese Laid-Open Patent Publication Hei-7/504676; *Cell Signals*, 7, 527 (1995);
50 *Mol. Pharmacol.*, 48, 416 (1995); *J. Med. Chem.*, 34, 624 (1991); and *J. Pharmacol. Exp. Ther.*, 272, 3 (1995)). However, those compounds have a problem in terms of their behavior *in vivo* such as poor transfer into blood and none of them have been put in the market as pharmaceuticals. Incidentally, there has been no report at all for the 7-amino-1-phenylpyrido[2,3-d]-pyrimidine-2,4-dione derivatives of the present invention.

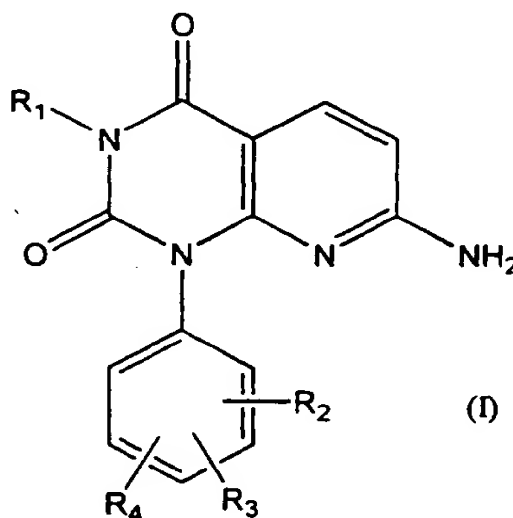
Problem and Solution

[0009] The problem underlying the invention of the present application is to solve the above-mentioned problems in prior art and is to offer a therapeutic agent for bronchial asthma which has been briskly demanded by patients and by medical fields, i.e. the agent having a high safety, a rapidly acting property and a good behavior *in vivo*.

[0010] The present inventors have carried out an intensive investigation for 7-aminopyrido[2,3-d]pyrimidine derivatives and have found that 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivatives have an excellent bronchial dilating action, have high safety and little side effect and exhibit good behavior *in vivo* whereupon the present invention has been achieved. Consequently, the compounds of the present invention are very useful as therapeutic agents for bronchial asthma.

Best Mode for Carrying Out the Invention

[0011] The present invention relates to 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivatives represented by the following formula (I) and pharmaceutically acceptable salts and hydrates thereof and it further relates to a therapeutic agent for bronchial asthma containing the said compound as an effective component.



wherein

R₁ is hydrogen, lower alkenyl, phenyl or lower alkyl which is optionally substituted with a substituent selected from

- (a) oxo,
- (b) lower alkoxy,
- (c) phenyl which is optionally substituted with one or more lower alkyl, lower alkoxy, carboxyl, lower alkoxy carbonyl, mercapto, halogen, trifluoromethyl and/or nitro;
- (d) naphthyl,
- (e) furyl,
- (f) isoxazolyl which is optionally substituted with one or more lower alkyl,
- (g) pyridyl which is optionally substituted with one or more lower alkyl and/or halogen,
- (h) thienyl which is optionally substituted with halogen, and
- (i) 1,3-dioxolanyl;

and R₂, R₃ and R₄ each independently is hydrogen, halogen, lower alkoxy, benzyloxy, carboxyl or lower alkoxy carbonyl.

[0012] In the formula, "lower alkyl" preferably means a linear or branched C₁₋₆-alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, hexyl, isohexyl or dimethylbutyl.

[0013] Also, "lower alkoxy" preferably represents a linear or branched C₁₋₆-alkoxy such as methoxy, ethoxy, pro-

poxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or t-butoxy, pentyloxy, isopentyloxy, neopentyloxy, t-pentyloxy, hexyloxy, isohexyloxy or dimethylbutoxy.

[0014] "Halogen" preferably is a fluorine, chlorine, bromine or iodine atom.

[0015] Finally, "lower alkenyl" preferably means a linear or branched C₂₋₆-alkenyl such as ethenyl, propenyl, butenyl, pentenyl or hexenyl.

[0016] Preferred embodiments of the present invention are given as follows.

(1) A 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivative of the above formula (I) and pharmaceutically acceptable salts and hydrates thereof.

(2) A compound according to (1) wherein R₂ is hydrogen.

(3) A compound according to (2) wherein R₃ is lower alkoxy.

(4) A compound according to (3) wherein R₃ is present in the meta-position of the aromatic ring.

(5) A compound according to any of (3) to (4) wherein lower alkoxy is methoxy.

(6) A compound according to any of (3) to (5) wherein R₄ is lower alkoxy.

(7) A compound according to (6) wherein R₄ is present in the meta-position of the aromatic ring.

(8) A compound according to any of (6) to (7) wherein lower alkoxy is methoxy.

(9) A compound according to any of (1) to (8) wherein R₁ is lower alkyl.

(10) A compound according to (9) wherein lower alkyl is isobutyl.

(11) A therapeutic agent for bronchial asthma comprising a compound according to any of (1) to (10) as an effective component.

(12) A bronchial dilator comprising a compound according to any of (1) to (10) as an effective component.

[0017] Especially, preferred compounds of the present invention are given as follows (the numbering of the compounds will be adhered to later on where applicable).

- (1) 7-amino-1,2,3,4-tetrahydro-1,3-diphenylpyrido[2,3-d]pyrimidine-2,4-dione
- (2) 7-amino-3-ethyl-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (3) 7-amino-1,2,3,4-tetrahydro-1-phenyl-3-propylpyrido[2,3-d]pyrimidine-2,4-dione
- (4) 7-amino-3-butyl-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (5) 7-amino-3-ethyl-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione
- (6) 7-amino-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-3-propylpyrido[2,3-d]pyrimidine-2,4-dione
- (7) 7-amino-3-butyl-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione
- (8) 7-amino-3-benzyl-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione
- (9) 7-amino-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-3-propylpyrido[2,3-d]pyrimidine-2,4-dione
- (10) 7-amino-3-butyl-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4-dione
- (11) 7-amino-3-benzyl-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4-dione
- (12) 7-amino-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-3-(4-picolyl)pyrido[2,3-d]pyrimidine-2,4-dione
- (13) 7-amino-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-3-propylpyrido[2,3-d]pyrimidine-2,4-dione
- (14) 7-amino-1-(2,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-3-propylpyrido[2,3-d]pyrimidine-2,4-dione
- (15) 7-amino-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-3-propylpyrido[2,3-d]pyrimidine-2,4-dione
- (16) 7-amino-3-benzyl-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (17) 7-amino-1,2,3,4-tetrahydro-1-phenyl-3-(4-picolyl)pyrido[2,3-d]pyrimidine-2,4-dione
- (18) 7-amino-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-3-(4-picolyl)pyrido[2,3-d]pyrimidine-2,4-dione
- (19) 7-amino-3-benzyl-1-(2,4-dimethoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione
- (20) 7-amino-1-(3,5-dimethoxyphenyl)-3-(2-ethoxyethyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione
- (21) 7-amino-3-(3-butenyl)-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione
- (22) Methyl [7-amino-1,2,3,4-tetrahydro-3-(4-picolyl)-2,4-dioxypyrido[2,3-d]pyrimidine-1-yl]-3-benzoate
- (23) 7-amino-3-(4-chlorobenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (24) 7-amino-1,2,3,4-tetrahydro-3-(2-methylpicolyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (25) 7-amino-1,2,3,4-tetrahydro-3-(2-picolyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (26) 7-amino-1,2,3,4-tetrahydro-3-(3-picolyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (27) 7-amino-3-(3-chlorobenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (28) 7-amino-1,2,3,4-tetrahydro-3-(4-methoxybenzyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (29) 7-amino-3-(4-fluorobenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (30) 7-amino-1,2,3,4-tetrahydro-3-(4-methylbenzyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (31) 7-amino-1,2,3,4-tetrahydro-3-(3-nitrobenzyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (32) 7-amino-3-(2-chlorobenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
- (33) 7-amino-1,2,3,4-tetrahydro-3-(3-methylbenzyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione

- (34) 7-amino-3-(3,4-dichlorobenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (35) 7-amino-1,2,3,4-tetrahydro-3-(3-methoxybenzyl)-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (36) 7-amino-1,2,3,4-tetrahydro-3-(4-trifluoromethylbenzyl)-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (37) 7-amino-1,2,3,4-tetrahydro-1-phenyl-3-(thienylmethyl)pyrido[2,3-d]pyrimidine-2,4-dione
 5 (38) 7-amino-3-(2-furfuryl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
 (39) 7-amino-1,2,3,4-tetrahydro-1-phenyl-3-(3-thienylmethyl)pyrido[2,3-d] pyrimidine-2,4-dione
 (40) 7-amino-3-(2-chloro-6-methylpicolyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (41) Methyl 4-[7-amino-1,2,3,4-tetrahydro-1-phenyl-2,4-dioxypyrido[2,3-d] pyrimidine-3-yl-methyl]benzoate
 (42) 7-amino-3-(2-dioxolanymethyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 10 (43) 4-[7-amino-1,2,3,4-tetrahydro-1-phenyl-2,4-dioxypyrido[2,3-d]pyrimidine-3-yl-methyl]benzoic acid
 (44) 7-amino-3-benzyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-2,4-dione
 (45) 7-amino-1,2,3,4-tetrahydro-3-(4-nitrobenzyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
 (46) 7-amino-1,2,3,4-tetrahydro-3-(2-methoxybenzyl)-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (47) 7-amino-3-(3,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 15 (48) 7-amino-3-(5-chlorothiénylmethyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (49) 7-amino-3-benzyl-1-(3,5-difluorophenyl)-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-2,4-dione
 (50) 7-amino-1,2,3,4-tetrahydro-3-(1-naphthylmethyl)-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (51) 7-amino-1,2,3,4-tetrahydro-3-(3,5-dimethylbenzyl)-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (52) 7-amino-3-benzyl-1,2,3,4-tetrahydro-1-(3-methoxyphenyl)pyrido[2,3-d] pyrimidine-2,4-dione
 20 (53) 7-amino-3-(4-bromobenzyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (54) 7-amino-3-(2-chloropicolyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione
 (55) 7-amino-3-benzyl-1-(3-benzoyloxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-2,4-dione
 (56) 7-amino-1,2,3,4-tetrahydro-3-(3-methylisoxazol-5-yl-methyl)-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
 (57) 7-amino-3-(3,5-dimethylisoxazol-4-yl-methyl)-1,2,3,4-tetrahydro-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione
 25 (58) 7-amino-1,2,3,4-tetrahydro-1-phenyl-3-(5-phenylpentyl)pyrido[2,3-d] pyrimidine-2,4-dione

[0018] In the above compounds of the present invention, the most preferred compound is 7-amino-1-(3,5-dimethoxyphenyl)-1,2,3,4-tetrahydro-3-propylpyrido[2,3-d]pyrimidine-2,4-dione (Compound 15).

[0019] The compounds of the present invention may be manufactured according to a method described in Japanese Laid-Open Patent Publication Sho-63/45279, Hei-8/3046, Hei-8/3164 or Hei-8/3165, and it will be further illustrated in detail by way of the following examples.

[0020] The compounds represented by the above-given formula (I) include the pharmaceutically acceptable salts of thereof such as acid addition salts with hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, perchloric acid, thiocyanic acid, boric acid, formic acid, acetic acid, haloacetic acid, propionic acid, glycolic acid, citric acid, tartaric acid, succinic acid, gluconic acid, lactic acid, malonic acid, fumaric acid, anthranilic acid, benzoic acid, cinnamic acid, p-toluenesulfonic acid, naphthalenesulfonic acid or sulfanilic acid; salts with alkali metal such as sodium or potassium, salts with alkaline-earth metal such as calcium or magnesium, or salts with other metals such as aluminum; or salts with bases such as ammonia or organic amines. Those salts may be manufactured by known methods from the compounds of the present invention in a free state or may be mutually converted among the salts. When there are steric isomers such as cis-trans isomer, optical isomer, conformational isomer and hydrate for the substances of the present invention, the present invention includes any and all of them.

[0021] The substance of the present invention can be made into pharmaceutical preparations by a combination with a suitable pharmaceutical carriers or diluents. Any of the known methods for providing preparations, such as for oral or parenteral administrations (e.g. solids, half-solids, liquids or gases) may be used to produce the pharmaceutical compositions of the present invention. In preparing the preparations, the substance of the present invention may be used in the form of their pharmaceutically acceptable salts, and also can be used either solely or jointly together with other pharmaceutically active components.

[0022] In the case of preparations for oral administration, the substance of the present invention as it is or together with commonly-used excipients such as a suitable additive (e.g. lactose, mannitol, corn starch, potato starch, etc.) is mixed with binders such as crystalline cellulose, cellulose, gum arabicum, corn starch, gelatin, etc., disintegrating agents such as corn starch, potato starch, potassium carboxymethylcellulose, etc., lubricating agents such as talc, magnesium stearate, etc. and others including bulking agents, moisturizing agents, buffers, preservatives, perfumes and the like to give tablets, diluted powders, granules or capsules.

[0023] Alternatively, suppositories may be prepared by mixing with fatty/oily bases (e.g. cacao butter), emulsified bases, water-soluble bases (e.g. macrogol), hydrophilic bases, etc.

[0024] In the case of injections, it is possible to prepare the solutions or the suspensions in an aqueous and non-aqueous solvents such as distilled water for injection, physiological saline solution, Ringer's solution, plant oil, synthetic fatty acid glycerides, higher fatty acid esters, propylene glycol, etc.

[0025] In case of inhalations or aerosol preparations, the compound of the present invention in the form of a liquid or minute powder can be filled up in an aerosol container with gas or liquid spraying agent, and if desired, with conventional adjuvants such as humidifying agents or dispersing agent. They can also be used as pharmaceuticals for a non-pressurized preparation such as in a nebulizer or an atomizer. It is also possible, depending upon the type of the disease, to prepare the pharmaceutical preparations which are other than those which were mentioned already and are suitable for the therapy such as, for example, collyriums, ointments, poultices, etc.

[0026] The preferred dose of the compound of the present invention may vary depending upon the object to be administered the patient, form of the preparation, method for the administration, term for the administration, etc. and, in order to achieve a desired effect, 0.001-50 mg per day, preferably 0.05-25 mg per day may be usually given to common adults by oral route. In the case of a parenteral administration such as by injection, it is preferred that, due to the influence of the absorption, etc., a level of from 1/3 to 1/10 of the above-given dose by oral route is administered.

[0027] The present invention will be further illustrated by way of the following examples although the present invention is not limited by them at all.

Examples

[0028] The starting materials may be purchased from Aldrich Chemical Co., Inc.; Furuka Chemical Inc.; Lancaster Synthesis Inc.; Maybridge Chemical Co., Ltd.; or Tokyo Kasei K.K. or may be synthesized by known methods mentioned in literatures such as *J. Org. Chem.*, **16**, 1879 (1951); *J. Am. Chem. Soc.*, **75**, 114 (1953); etc.

Example 1

(1) Manufacture of 6-amino-5-formyl-1,3-diphenyluracil.

[0029] A solution of 6-amino-1,3-diphenyluracil (10.0 g, 35.8 mmol) in dimethylformamide (100 mL) was cooled in an ice bath and phosphorus oxychloride (3.7 mL, 39.4 mmol) was dropped thereinto using a dropping funnel. The reaction mixture was stirred at room temperature for two hours and the reaction was stopped by adding 50 mL of water thereto. The pH was adjusted to 10 by a 1N solution of potassium hydroxide and stirring was carried out at room temperature for additional one hour. Crude crystals separated out therefrom were filtered and, after washing with 100 mL of water, the crude crystals were filtered. The resulting crude crystals were further recrystallized from hexane and ethyl acetate to give 6-amino-5-formyl-1,3-diphenyluracil (2.2 g) in a 40% yield (Mp: 141-142°C).

¹H-NMR (DMSO-d₆) δ: 7.29-7.61 (m, 10H), 9.80 (s, 1H), 9.98 (s, 1H)
IR (KBr): 3309, 1730, 1662, 1647, 1616, 1516, 1491, 1365, 770, 692 cm⁻¹

Analysis:	Calculated for C ₁₇ H ₁₃ N ₃ O ₃ :	C, 66.44;	H, 4.26;	N, 13.67
	Found:	C, 66.59;	H, 4.24;	N, 13.77

MS (EI) m/z: 307 [M⁺], 279, 160, 132, 77

(2) Manufacture of 7-amino-1,2,3,4-tetrahydro-1,3-diphenylpyrido[2,3-d]pyrimidine-2,4-dione (Compound 1).

[0030] A solution of 6-amino-5-formyl-1,3-diphenyluracil (5.0 g, 16.3 mmol) and 2-(triphenylphosphoranylidene)acetonitrile (5.9 g, 19.6 mmol) in anhydrous acetonitrile (100 mL) was heated to reflux for 24 hours in an argon stream. The reaction mixture was allowed to cool and the solvent was evaporated therefrom *in vacuo*. The crude crystals separated out therefrom were recrystallized from benzene to give 7-amino-1,2,3,4-tetrahydro-1,3-diphenylpyrido[2,3-d]pyrimidine-2,4-dione (2.4 g) in a 45% yield (Mp: 162-163°C).

¹H-NMR (DMSO-d₆) δ: 6.33 (d, 1H, J=9Hz), 6.89 (br, 2H), 7.31-7.93 (m, 10H), 7.93 (d, 1H, J=9Hz)
IR (KBr): 3358, 1709, 1660, 1624, 1427, 1398, 694 cm⁻¹

Analysis:	Calculated for $C_{19}H_{14}N_4O_2$:	C, 69.08;	H, 4.27;	N, 16.96
	Found:	C, 68.99;	H, 4.37;	N, 16.97

MS (EI) m/z : 330 $[M^+]$, 211

[0031] Appropriate starting materials were used in place of 6-amino-1,3-diphenyluracil which was the starting material in the above Example 1 and subjected to a method mentioned in Example 1 in the same manner whereupon the Compounds 2 to 58 represented by the following formula (II) were manufactured. Details of the compounds are mentioned in Table 1.

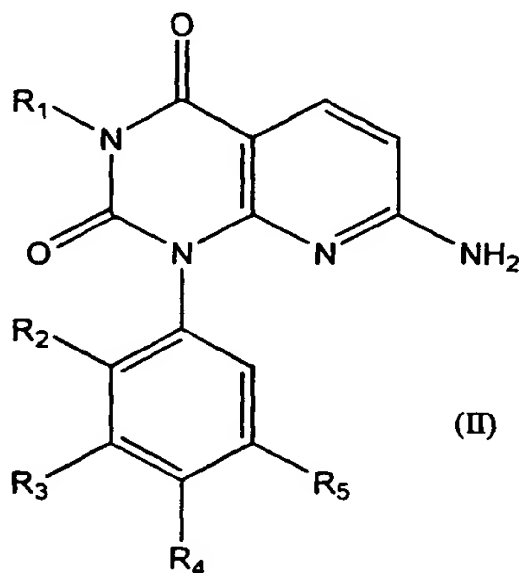


Table 1

Comp. No.	R ₁	R ₂	R ₃	R ₄	R ₅	Mp (°C)
2	Et	H	H	H	H	218 - 219
3	Pr	H	H	H	H	198 - 199
4	Bu	H	H	H	H	209 - 211
5	Et	H	OMe	H	OMe	274 - 275
6	Pr	H	OMe	H	OMe	240 - 241
7	Bu	H	OMe	H	OMe	228 - 230
8	Bn	H	OMe	H	OMe	236 - 237
9	Pr	H	H	OMe	H	199 - 201
10	Bu	H	H	OMe	H	145 - 146
11	Bn	H	H	OMe	H	249 - 251
12	4-picolylyl	H	H	OMe	H	288 - 289
13	Pr	H	OMe	OMe	H	219 - 221
14	Pr	OMe	H	H	OMe	271 - 272
15	iso-Bu	H	OMe	H	OMe	206 - 208
16	Bn	H	H	H	H	261 - 262
17	4-picolylyl	H	H	H	H	280 - 281
18	4-picolylyl	H	OMe	H	OMe	225 - 227
19	Bn	OMe	H	OMe	H	254 - 256
20	EtOEt	H	OMe	H	OMe	225 - 227
21	3-butenyl	H	OMe	H	OMe	215 - 217
22	4-picolylyl	H	COOMe	H	H	250 - 251
23	4-Cl-Bn	H	H	H	H	240 - 241
24	3-(2-Me-picolylyl)	H	H	H	H	286 - 288
25	2-picolylyl	H	H	H	H	236 - 237
26	3-picolylyl	H	H	H	H	> 300
27	3-Cl-Bn	H	H	H	H	230 - 231
28	4-MeO-Bn	H	H	H	H	248 - 250
29	4-F-Bn	H	H	H	H	224 - 226
30	4-Me-Bn	H	H	H	H	224 - 225
31	3-NO ₂ -Bn	H	H	H	H	247 - 248
32	2-Cl-Bn	H	H	H	H	262 - 263

Table 1 (cont.)

Comp. No.	R ₁	R ₂	R ₃	R ₄	R ₅	Mp (°C)
33	3-Me-Bn	H	H	H	H	248 - 249
34	3,4-Cl ₂ -Bn	H	H	H	H	245 - 246
35	3-MeO-Bn	H	H	H	H	247 - 248
36	4-CF ₃ -Bn	H	H	H	H	170 - 173
37	2-thienylmethyl	H	H	H	H	279 - 282
38	2-furfuryl	H	H	H	H	265 - 268
39	3-thienylmethyl	H	H	H	H	276 - 280
40	3-(2-Cl-6-Me-picolyl)	H	H	H	H	243 - 245
41	4-COOMe-Bn	H	H	H	H	242 - 244
42	2-dioxoranylmethyl	H	H	H	H	265 - 267
43	4-COOH-Bn	H	H	H	H	> 300
44	Bn	H	Cl	H	H	254 - 256
45	4-NO ₂ -Bn	H	H	H	H	245 - 248
46	2-MeO-Bn	H	H	H	H	> 300
47	3,5-(MeO) ₂ -Bn	H	H	H	H	224 - 225
48	2-(5-Cl-thienyl)-methyl	H	H	H	H	251 - 254
49	Bn	H	F	H	F	253 - 255
50	(1-naphthyl)-methyl	H	H	H	H	> 300
51	3,4-Me ₂ -Bn	H	H	H	H	243 - 244
52	Bn	H	OMe	H	H	222 - 225
53	4-Br-Bn	H	H	H	H	249 - 250
54	3-(2-Cl-picolyl)	H	H	H	H	258 - 259
55	Bn	H	OBn	H	H	213 - 215
56	5-(3-Me-isoxazolyl)-methyl	H	H	H	H	250 - 251
57	4-(3,5-Me ₂ -isoxazolyl)-methyl	H	H	H	H	253 - 254
58	5-Ph-pentyl	H	H	H	H	135 - 137

Example 2: Relaxing Action to Smooth Muscle of Airway of Guinea Pigs.

[0032] A guinea pig was killed by draining out the blood, airway was isolated, and four airway pieces having a width of about 1 cm cut along the cartilage were connected by silk yarn to prepare an airway smooth muscle sample. The sample was hung with a load of about 0.5 g in a 5-mL Magnus vessel filled with a Tyrode solution and aerated with a mixed gas (95% O₂ and 5% CO₂).

[0033] After the sample was allowed to stand for 30 minutes to one hour, it was treated with histamine (final concentration: 10⁻⁵M) and the constriction was recorded on a recorder via an isotonic transducer. This was repeatedly treated with 10⁻⁵M of histamine and, after confirming that the constriction became constant, it was treated with 10⁻⁴ M of histamine.

[0034] After the maximum constriction reaction of the smooth muscle became constant, the test compound was added thereto starting from low concentration cumulatively to investigate the relaxing action. A dose vs. reaction curve was prepared from the isotonic reaction of various concentrations of the test compound and ED₅₀, a concentration showing 50% of the maximum reaction, was determined.

[0035] 7-Amino-1,3-diethyl-1,2,3,4-tetrahydropyrido-[2,3-d]pyrimidine-2,4-dione (Control Compound A; a compound mentioned in the Japanese Laid-Open Patent Publication Hei-8/3046), 5-amino-1,3-diethyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-1,4-dione (Control Compound B; a compound mentioned in the Japanese Laid-Open Patent Publication Sho-63/45279) and theophylline were used as control agents.

[0036] An example of the result is shown in Table 2. The compounds of the present invention showed better efficacy than the known bronchial dilators when tested by a relaxing action to airway smooth muscle isolated from guinea pigs.

Table 2

Compound No.	EC ₅₀ (μM)
5	1.7
6	0.40
7	0.59
8	0.32
15	0.21
16	0.023
17	0.019
18	0.061
28	0.045
29	0.076
37	0.021
38	0.040
39	0.027
Control Compound A	1.01
Control Compound B	0.83
theophylline	51

Example 3: Influence on Continuous Constriction of Airway Smooth Muscle of Rats.

[0037] The back of the head of rat was struck to cause a cerebral concussion, carotid arteries on both sides were immediately cut and the pulmonary main artery was isolated. The isolated artery was fully aerated with a mixed gas (95% O₂ and 5% CO₂), placed in a Krebs-Henseleit solution warmed at 37°C, excessive tissues were removed as much as possible and a spiral sample (having a width of about 2 mm and a length of 15 mm) was prepared according to a method of Furchgott, et al. The blood vessel sample was hung with a load of about 0.5 g in a 5-mL Magnus vessel filled with a Krebs-Henseleit solution and aerated with a mixed gas (95% O₂ and 5% CO₂).

[0038] After the sample was allowed to stand for 30 minutes to one hour, it was treated with noradrenaline (final

concentration: 10^{-7} M) and the constricting reaction was amplified via an amplifier for blood pressure using an FD pickup and recorded on a recorder. Noradrenaline (10^{-7} M) was repeatedly applied and, after confirming that the constriction became constant, 10^{-7} M of noradrenaline was applied.

[0039] After the maximum shrinking reaction of the smooth muscle became constant and the test compound was added thereto starting from the low concentration cumulatively to investigate the relaxing action. A dose vs. reaction curve was prepared from the isotonic reaction of various concentrations of the test compound and an ED_{50} , a concentration showing 50% of the maximum reaction, was determined.

[0040] An example of the result is shown in Table 3. The compounds of the present invention showed little affection to blood vessel and high safety when tested by an influence on a continuous constriction of smooth muscle of blood vessel isolated from rats.

Table 3

Compound No.	EC_{50} (μ M)
5	>100
6	>100
15	>100
16	50.1
18	>100

Example 4: Influence on General Symptoms of Mice.

[0041] Mice having no abnormality in their appearance before administration of the test drugs were selected, and five mice were used for each group. Oral administration of the test compound was carried out and, 30 minutes, one hour and two hours thereafter, observations were conducted according to the modified method of Irwin's method for observing the general symptoms of mice. Degree of the symptom was evaluated in terms of (+) and (-) and, when the symptom was apparently severe, it was mentioned as (++). Incidentally, death was observed until the next day of the administration.

1) Suppression of spontaneous motility: When mice were transferred from a home cage to a cage for symptom observation and, if motion of the mice was less than the non-administered group at that time, that was evaluated as (+).

2) Muscle relaxation: When forefeet of mice were hung on a wire stretched horizontally so that the mice were hung by means of the forefeet and, if their reaction at that time for climbing up the wire took longer time than the non-administered group, that was evaluated as (+).

3) Passiveness: When mice were hung by holding the neck of the mice between two fingers and, if the mice did not move so much at that time, that was marked as (+).

4) Blepharoptosis: If 1/4 or more was closed as compared with the non-administered group, that was evaluated as (+).

5) Salivation: If salivation was noted a little around the mouth, that was evaluated as (+).

6) Death: If dead case was noted, that was mentioned as such.

[0042] 5-Amino-1,3-diethyl-1,2,3,4-tetrahydropyrido[2,3-d]-pyrimidine-2,4-dione (Control Compound B; a compound mentioned in the Japanese Laid-Open Patent Publication Sho-63/45279) was used as a control drug.

[0043] An example of the result is shown in Table 4. When the compounds of the present invention were tested in terms of an influence on the general symptoms of mice, they showed very high safety as compared with the known bronchial dilator having the similar structure.

Table 4

Comp No	admin. dose (mg/kg)	Suppr. of spontaneous motility	Muscle relaxation	Passiveness	Blepharoptosis	Salivation	Death
5	1000	(+) × 2	(+) × 3	(-)	(+) × 3	(-)	0
6	300	(+) × 1	(-)	(-)	(+) × 1	(-)	0
	1000	(+) × 2	(+) × 2	(-)	(+) × 2	(-)	0
7	300	(+) × 2	(+) × 2	(-)	(+) × 1	(-)	0
	1000	(+) × 1	(+) × 3	(-)	(-)	(-)	0
		(++) × 1					
Control Comp. B	100	(+) × 3	(+) × 3	(+) × 1	(+) × 2	(-)	0
	300	(+) × 3	(+) × 4	(+) × 1	(+) × 2	(-)	0
			(++) × 1	(++) × 2	(++) × 1		

Example 5: Concentration in Blood of Guinea Pigs.

[0044] Each test substance was orally administered at the dose of 30 mg/kg. It was suspended in 1% methyl cellulose and made into a preparation so as to make the administering dose 5 mL/kg.

[0045] A group consisted of four animals and blood was collected after 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 24 hours from the administration (A feed was given after collection of the blood after 6 hours). Thus, each about 200 mL (corresponding to four capillary tubes) of blood were collected with intervals using a heparin-treated capillary tube and plasma was separated by a hematocrit centrifuge to prepare a plasma sample. A plasma sample of about 100 mL was preserved at -80°C until the measurement.

[0046] Methanol (200 mL) was added to 100 mL of the plasma followed by mixing, the mixture was centrifuged at 1500 × g for ten minutes at 40°C and the separated supernatant liquid was filtered through a membrane filter of 0.5 mm. The filtrate was used as a sample for an HPLC, analyzed under the analyzing condition that the column was 100 mm × 4.6 mm (inner diameter) of TSK-gel Super ODS, the flow rate was 1.0 mL/minute, the column temperature was 40°C, an injection amount was 6 mL, detection was done by UV of 225 nm and the mobile phase was water-acetonitrile (75:25 in terms of % by volume) and the maximum concentration in blood (C_{max}), time required for achieving the maximum concentration in blood (T_{max}), half life in blood ($T_{1/2}$) and area under a curve of concentration in blood vs. time (AUC 0-lim) were determined.

[0047] RS-25344 (*Cell Signal*, 7(5), 527 (1995); *Mol. Pharmacol.*, 48(4), 616 (1995)) and CR-77059 (*J. Med. Chem.*, 34, 624 (1991); *J. Pharmacol. Exp. Ther.*, 272, 3 (1995)) were used as control drugs.

[0048] An example of the result is shown in Table 5. When the behavior in blood of guinea pigs was tested, the compounds of the present invention showed a good transfer into blood and a long half life exhibiting a favorable behavior *in vivo* as compared with known xanthine-related compounds having similar structures.

Table 5

Compound No.	C_{max} (μg/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC 0-lim (μg h/mL)
5	30.0	3.0	12.1	458.2
6	13.7	4.0	28.4	255.8
7	1.6	15.0	131.4	28.6
15	10.1	2.3	9.8	133.8
RS-25344	(less than identification limit)			
CP-77059	(less than identification limit)			

Advantage of the Invention

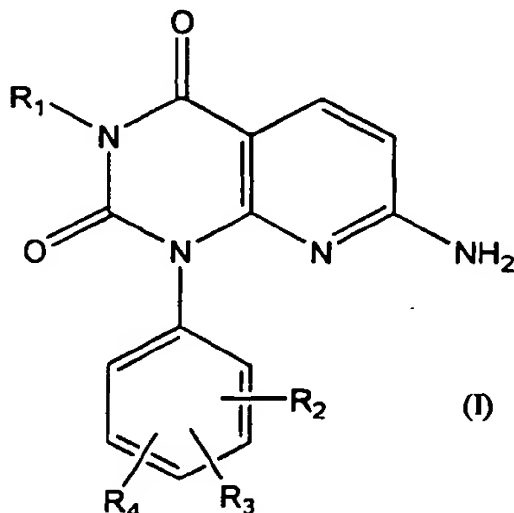
[0049] As shown in Table 2, the 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivatives of the present invention exhibit better bronchial dilating action than the known bronchial dilators having the similar structures. Accordingly, the compounds of the present invention are useful as therapeutic agents for bronchial asthma.

[0050] It is also apparent from Tables 3 and 4 that the compounds of the present invention show far higher safety than the known bronchial dilators having the similar structures. It is further apparent from Table 5 that the compounds of the present invention show a good transfer into blood and a long half life in blood which are not available in the known xanthine-related compounds whereby a favorable behavior *in vivo* is achieved. Accordingly, the compounds of the present invention have far better characteristics as pharmaceuticals than the known compounds having the similar structures.

[0051] As mentioned above, the compounds of the present invention have an excellent bronchial dilating action, a high safety and little side effect whereby they are the compounds solving the problems in the prior art. Moreover, the compounds of the present invention exhibit a favorable behavior *in vivo* and their usefulness as pharmaceuticals is quite high.

Claims

1. A 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivative of the formula (I) or a pharmaceutically acceptable salt or hydrate thereof



wherein

R₁ is hydrogen, C₂₋₆-alkenyl, phenyl or C₁₋₆-alkyl which is optionally substituted with a substituent selected from

- (a) oxo,
- (b) C₁₋₆-alkoxy,
- (c) phenyl which is optionally substituted with one or more C₁₋₆-alkyl, C₁₋₆-alkoxy, carboxyl, (C₁₋₆-alkoxy)carbonyl, mercapto, halogen, trifluoromethyl and/or nitro;
- (d) naphthyl,
- (e) furyl,
- (f) isoxazolyl which is optionally substituted with one or more C₁₋₆-alkyl,
- (g) pyridyl which is optionally substituted with one or more C₁₋₆-alkyl and/or halogen,
- (h) thienyl which is optionally substituted with halogen, and
- (i) 1,3-dioxolanyl;

and R₂, R₃ and R₄ each independently is hydrogen, halogen, C₁₋₆-alkoxy, benzyloxy, carboxyl or (C₁₋₆-

alkoxy)carbonyl.

2. Compound according to claim 1, wherein R_2 is hydrogen.
- 5 3. Compound according to claim 1 or 2, wherein R_3 and/or R_4 is C_{1-6} -alkoxy.
4. Compound according to claim 3, wherein R_3 and/or R_4 is present in the metaposition of the aromatic ring.
5. Compound according to claim 3 or 4, wherein the C_{1-6} -alkoxy is methoxy.
- 10 6. Compound according to any of claims 1 to 5, wherein R_1 is C_{1-6} -alkyl.
7. Pharmaceutical composition comprising a 7-amino-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione derivative according to any of the claims 1 to 6 as an effective component.
- 15 8. Use of a 7-amino-1-phenylpyrido[2,3-d] pyrimidine-2,4-dione derivative according to any of the claims 1 to 6 for the preparation of a medicament effective in the treatment of bronchial asthma or as a bronchial dilator

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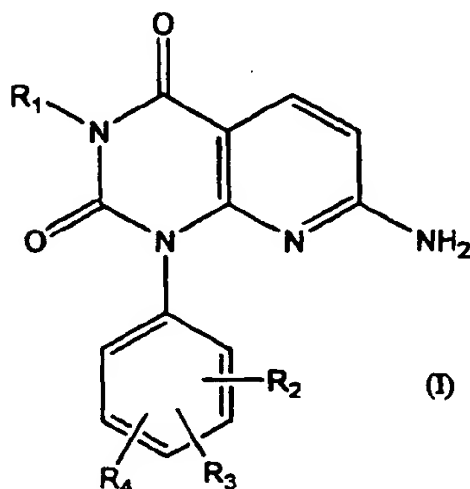
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(54) **7-Aminopyrido(2,3-d)-pyrimidine derivatives for treatment of bronchial asthma**

(57) The invention provides 7-amino-1-phenylpyrido[2,3-d]pyrimidine-2,4-dione derivatives of the formula (I) or a pharmaceutically acceptable salt or hydrate thereof;



wherein

R₁ is hydrogen, lower alkenyl, phenyl or optionally substituted lower alkyl which is optionally substi-

tuted with a substituent selected from oxo; lower alkoxy; phenyl which is optionally substituted with one or more lower alkyl, lower alkoxy, carboxyl, lower alkoxy carbonyl, mercapto, halogen, trifluoromethyl and/or nitro; naphthyl; furyl; isoxazolyl which is optionally substituted with one or more lower alkyl; pyridyl which is optionally substituted with one or more lower alkyl and/or halogen; thienyl which is optionally substituted with halogen; and 1,3-dioxolanyl; and

R₂, R₃ and R₄ each independently is hydrogen, halogen, lower alkoxy, benzyloxy, carboxyl or lower alkoxy carbonyl,

which is useful for a therapeutic agent for bronchial asthma by exhibiting excellent bronchial dilating action as well as high safety and a favorable behavior *in vivo*.

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EUROPEAN SEARCH REPORT

Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (sICL7)
Y,D	EP 0 696 590 A (NIPPON ZOKI PHARMACEUTICAL CO) 14 February 1996 (1996-02-14) pages 6 and 7, compounds 17 and 67	1-8	C07D471/04 A61K31/505 A61P11/08 //(C07D471/04, 239:00,221:00)
Y,D	WO 93 19068 A (SYNTEX INC) 30 September 1993 (1993-09-30) * claim 6 *	1-8	
Y	EP 0 260 817 A (PFIZER) 23 March 1988 (1988-03-23) * page 5; example 1 *	1-8	
Y	MULLER T ET AL: "Subtypes of the type 4 cAMP phosphodiesterases: structure, regulation and selective inhibition" TRENDS IN PHARMACOLOGICAL SCIENCES, 88, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 17, no. 8, 1 August 1996 (1996-08-01), pages 294-298, XP004034578 ISSN: 0165-6147 * page 298 *	1-8	
Y	EP 0 163 599 A (NIPPON ZOKI PHARMACEUTICAL CO) 4 December 1985 (1985-12-04) * page 4, line 19 *	1-8	TECHNICAL FIELDS SEARCHED (sICL7)
A	US 3 272 816 A (PAPESEH) 13 September 1966 (1966-09-13) see formula in column 1	1-8	C07D A61K A61P
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 31 March 2000	Examiner Steendijk, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document</p> <p>T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document</p>			

EP 0 994 113 A3 (PUB. INT.)

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31-03-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0696590 A	14-02-1996	JP 8003046 A	09-01-1996
		JP 8003164 A	09-01-1996
		JP 8003165 A	09-01-1996
		AU 694958 B	06-08-1998
		AU 2175295 A	04-01-1996
		CA 2151971 A	18-12-1995
		CN 1120436 A	17-04-1996
		US 5776942 A	07-07-1998
WO 9319068 A	30-09-1993	US 5264437 A	23-11-1993
		AU 3918693 A	21-10-1993
		CA 2132297 A	30-09-1993
		CN 1078470 A,B	17-11-1993
		EP 0631580 A	04-01-1995
		FI 944305 A	16-09-1994
		HU 67552 A	28-04-1995
		HU 9500114 A	28-06-1995
		IL 105092 A	15-06-1998
		JP 7504676 T	25-05-1995
		MX 9301530 A	31-01-1994
		NO 943456 A	16-09-1994
		NZ 251525 A	25-09-1996
		ZA 9301945 A	18-09-1994
EP 0260817 A	23-03-1988	US 4797403 A	10-01-1989
		WO 8801270 A	25-02-1988
		AT 63553 T	15-06-1991
		GR 3002065 T	30-12-1992
		IE 59937 B	04-05-1994
		IN 168876 A	29-06-1991
		US 4880810 A	14-11-1989
		AT 388378 B	12-06-1989
		AU 579047 B	10-11-1988
		AU 7724787 A	10-03-1988
		CA 1294618 A	21-01-1992
		CN 1014992 B	04-12-1991
		CS 8705974 A	12-05-1989
		DD 261598 A	02-11-1988
		DK 433787 A	22-02-1988
		EG 18270 A	30-12-1992
		FI 873608 A,B,	22-02-1988
		HU 44786 A	28-04-1988
		IL 83569 A	15-12-1991
		JP 1898116 C	23-01-1995
		JP 6025166 B	06-04-1994
		JP 63060974 A	17-03-1988

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ON EUROPEAN PATENT APPLICATION NO.**

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31-03-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0260817 A		KR 9003497 B	21-05-1990
		MX 7829 A	01-08-1993
		NO 873514 A, B,	22-02-1988
		NZ 221502 A	28-11-1989
		PH 23853 A	23-11-1989
		PT 85555 A, B	01-09-1987
		SU 1769758 A	15-10-1989
		ZA 8706172 A	29-03-1989
EP 0163599 A	04-12-1985	JP 1855719 C	07-07-1994
		JP 5059118 B	30-08-1993
		JP 60226882 A	12-11-1985
		AT 51231 T	15-04-1990
		US 4886807 A	12-12-1989
US 3272816 A	13-09-1966	NONE	

EPO FORM P/99

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82